REPLACED BY ART 34 AMDT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A158107	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/04763	International filing date *(day/month/year)* 27.10.2003	Priority date *(day/month/year)* 31.10.2002
International Patent Classification (IPC) or both national classification and IPC C07C281/18		
Applicant LABORATORIOS VITA, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.05.2004	27.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heibl, C Telephone No. +49 89 2399-8331

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/04763

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10 received on 21.05.2004 with letter of 17.05.2004

Claims, Numbers

1-7 received on 21.05.2004 with letter of 17.05.2004

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V ----------

The preparation of lamotrigine (i.e. the compound of formula I) involves usually cyclisation of an aminoguanidine acetonitrile derivative of formula II. This intermediate is prepared by reacting 2,3-dichlorobenzoyl cyanide with aminoguandine bicarbonate in acidic medium. Generally, the acid is nitric or sulphuric acid.

According to EP-A 1 127 873 (D1), the latter reaction is very slow, due to the nature of the acid. In order to improve this, D1 teaches the use of polyphosphoric acid. The present application is seen as providing a further process for this purpose.

The solution provided consists of the use of methanesulfonic acid as the only reaction medium. As shown in the examples, this may be regarded as a suitable solution of the above-mentioned problem.

The use of p-toluenesulfonic acid (together with sulfuric acid) in the same reaction is known from WO-A 01/49669 (D2; see page 12, lines 20-21, and claim 8).
However, the reaction medium of D2 is still aqueous, and D2 is silent on any possible spreading of the use of p-toluenesulfonic acid to that of methanesulfonic acid.
Therefore, the present use cannot be regarded as having been described or fairly suggested in the available (pre-published) prior art.
In addition, it appears that the present process has advantages over D1 and D2: Essentially the fact that it uses no additional solvent (thereby also avoiding environmental problems) gives rise to shorter reaction times and better yields.
Therefore, the claimed process(es) may also be regarded as involving an inventive step.

The subject-matter of present claims 1-7 is thus considered to meet the criteria of Art. 33(2)-(4) PCT.

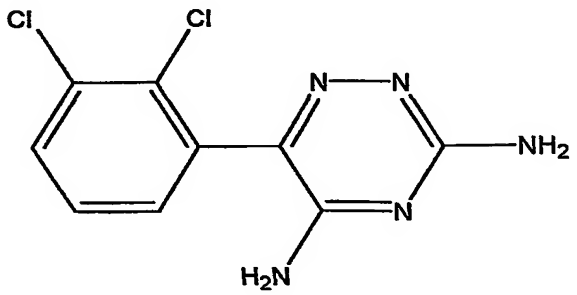
Process for preparing a pharmaceutically active compound and for preparing its intermediate

Field of the invention

This invention relates to a new method for preparing an intermediate useful in turn for preparing a pharmaceutically active compound with antiepileptic properties, and a method for making said pharmaceutically active compound.

Background of the invention

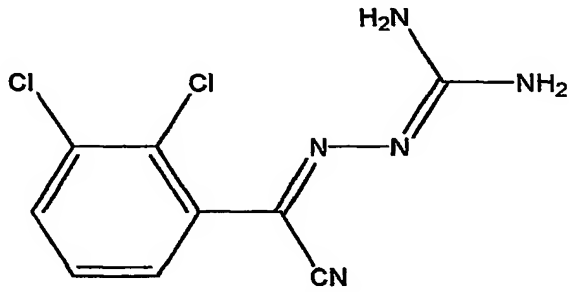
Patent EP 21121 describes 3,5-diamino-6-(substituted phenyl)-1,2,4-triazines which are active in central nervous system disorders such as psychiatric and neurological disorders, and are particularly useful as anticonvulsants, for example in the treatment of epilepsy. Of these, the preferred compound is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, of formula (I):



(I)

This compound is commonly known as lamotrigine and is marketed as an anti-epileptic drug.

The said European patent discloses the preparation of lamotrigine by the reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate to give the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, of formula (II):



(II)

which by cyclisation, in an aliphatic alcohol under reflux in the presence of a strong base, yields lamotrigine.

The preparation of the intermediate of formula (II) by reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate is carried out in said patent EP 21121 in an aqueous solution of nitric acid in the presence of dimethyl sulphoxide. Subsequently, patents EP 247892, EP 963980 and WO 0035888 described the same reaction for preparing the intermediate of formula (II), but in this case in an aqueous solution of sulphuric acid and with acetonitrile as solvent.

The method described for preparing said intermediate nevertheless has disadvantages of an environmental type, since it uses solvents such as dimethyl sulphoxide and acetonitrile, and of an economic type due to it being an excessively slow reaction. In the aqueous medium in which the reaction is carried out and under the conditions described in that method, the 2,3-

dichlorobenzoyl cyanide has a tendency to hydrolyse and its reaction with aminoguanidine bicarbonate is too slow, requiring 2 to 7 days, after which time the yield obtained is only 15% to 60%.

European patent application EP 1127873 has the object of improving said method for preparing the intermediate by carrying out the reaction in a non-aqueous medium using polyphosphoric acid and with acetonitrile as solvent. However, this method still presents the same environmental disadvantages, since it also uses toxic solvents, as well as economic disadvantages in that, although the reaction time has been reduced to approximately 20 h, the reaction remains slow.

International patent application WO 0149669 describes the same reaction for preparing the intermediate of formula (II) using 2,3-dichlorobenzoyl cyanide and aminoguanidine bicarbonate, but in this case in the presence of concentrated sulphuric acid and *p*-toluenesulphonic acid in toluene at 80°C. Although under such conditions a reduced reaction time is achieved, it is nevertheless necessary to employ high temperatures, with the disadvantages this entails, such as the formation of decomposition or degradation by-products. Moreover, this method still has disadvantages of an economic type, since the yields obtained are of the order of 50%.

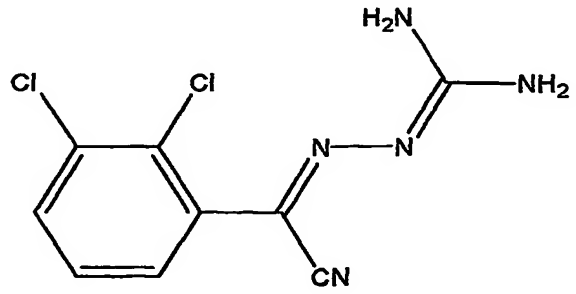
Furthermore, in the methods described above for preparing the intermediate, once the reaction has finished the acid suspension is filtered directly, without taking into account the traces of hydrogen cyanide produced as a reaction by-product.

The preparation of lamotrigine by cyclisation of the intermediate of formula (II), as noted above, was initially disclosed in patent EP 21121, refluxing in an alcohol in the presence of a strong base. This cyclisation reaction was subsequently disclosed in aliphatic alcohol under reflux in the absence of a base in the following European patents: EP 247892, EP 963980, EP 1127873. However, in order to prepare an end product of high purity, patents EP 963980, WO 0035888 and WO 0149669 disclosed that following such cyclisation one or more steps of recrystallisation are required, with the disadvantages this involves, such as yield losses, following which disclosed purities of only 99.1%, or at best 99.7%, are achieved.

Due to all this, and taking account of the prior art described, it is still necessary provide a method for preparing the intermediate of formula (II) and, therefore, of preparing lamotrigine, which is fast, cheap, safe and offers good yields.

Description of the invention

A first aspect of this invention is to provide a new method for preparing the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, of formula (II):



(II)

which comprises the reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate, characterised in that it is carried out in a non-aqueous medium in the presence of methanesulfonic acid.

Surprisingly, the authors of this invention have found that the use of methanesulphonic acid in preparing the intermediate of formula (II) means that the presence of other solvents as reaction medium is not required, for the acid itself acts as reaction medium, giving rise to good yields and shorter reaction times.

The method of the invention thus overcomes the problems related with the use of solvents not recommended for use on an industrial scale due to their harmful effects for the environment. The method also allows the reaction volume to be reduced.

Alternatively, it is also possible to dissolve the initial reagent, 2,3-dichlorobenzoyl cyanide, in a solvent that permits the preparation of concentrated solutions of 2,3-dichlorobenzoyl cyanide and in which the intermediate of formula (II) is not soluble, such as toluene.

Although the method of the invention can be carried out within a temperature range of 20-80°C, it is preferable for the reaction to take place at a temperature between 30° and 60°C. This means it is a reaction that occurs at low temperatures and is, therefore, a cheaper method.

Advantageously, the method of the invention permits preparation of the intermediate of formula (II)

with high yields, of the order of 80%, at low temperatures, and in only some 5 h.

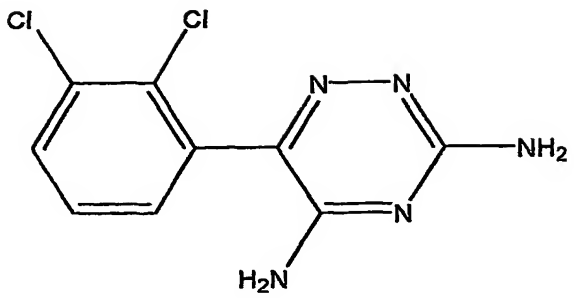
Preferably, the method of the invention comprises, once the reaction has finished and before filtering and isolation of the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, of formula (II), by conventional methods, an additional step that comprises the addition of water and subsequent adjustment of the pH of the medium until a pH higher than the pKa of the hydrogen cyanide (9.31)is achieved.

Preferably, the pH is adjusted by adding an aqueous solution of a strong base such as sodium hydroxide.

Advantageously, the fact that the pH of the medium is adjusted to a pH higher than the pKa of the hydrogen cyanide allows the traces of hydrogen cyanide produced in the reaction to be neutralised, which ensures filtering and isolation of the reaction product under safe conditions.

This invention also relates to a method for preparing lamotrigine which comprises preparation of the intermediate of formula II as defined in the first aspect of the invention.

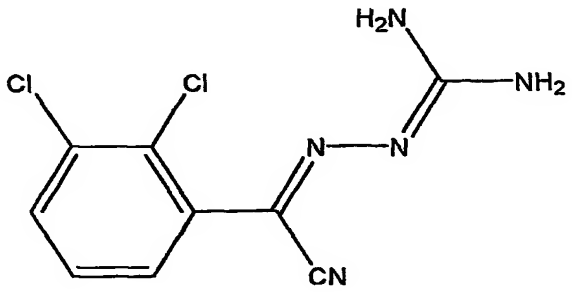
A second aspect of this invention is therefore to provide a method for preparing the 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, which comprises the following steps:

a) reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in non-aqueous medium in the presence of methanesulphonic acid, to give the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, of formula (II):



(II)

b) cyclisation of the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile of formula (II) in an aliphatic alcohol or in an aliphatic alcohol/water solution under reflux and,

if desired, obtaining a pharmaceutically acceptable salt thereof.

Preferably, said step b) is carried out by refluxing in an aliphatic alcohol. More preferably still, said aliphatic alcohol is chosen from between ethanol and isopropanol.

Advantageously, the preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine of formula (I) from the intermediate of formula (II) prepared according to the first aspect of the invention, permits a method to be carried out for preparing the compound of formula (I) with high yields and with a very high purity, even exceeding 99.9%, without any need for recrystallisation. All it needs is a washing to eliminate possible colouration from the end product.

Experimental Part

Provided below, by way of non-restrictive explanation of the invention, are the following examples.

EXAMPLES OF SYNTHESIS

Example 1: 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile

400 g (2 moles) of 2,3-dichlorobenzoyl cyanide are added to a mixture prepared from 333.6 g (2.45 moles) of aminoguanidine bicarbonate in 800 mL of methanesulphonic acid. The mixture is then heated at 45°C for 5 hours, cooled to 10°C and 2.4 L of water is added slowly, controlling exothermy at 20-30°C. The mixture is then adjusted to pH 11 with a 50% NaOH solution, filtered, the solid washed with water and dried at 45°C to yield 419.8 g (82%) of the product of the title.

NMR ^1H (DMSO), δ (ppm): 6.5- 6.9 (s, 4H, $-N=C(NH_2)_2$), 7.4 (t, 1H, ArH), 7.6 (d, 2H, ArH). M.p.= 180-183°C.

Example 2: 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile

To a mixture prepared from 4.2 g (0.031 moles) of aminoguanidine bicarbonate in 10 mL of methanesulphonic acid is added a solution of 5 g (0.025 moles) 2,3-dichlorobenzoyl cyanide in 5 mL of toluene. The mixture is heated at 45°C for 10 hours, cooled to 10°C and 30 mL of water added slowly, controlling exothermy at 20-30°C. The mixture is then adjusted to pH 11 with a 40% NaOH solution, filtered, the solid washed with water and dried at 45°C to yield 5.05 g (79 %) of the product of the title.

Example 3: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

A mixture made up of 100 g of 2-(2,3-dichlorophenyl)-2-(aminoguanidine)-acetonitrile cyanide as prepared in Example 1 and 1000 mL of absolute ethanol is heated under reflux for 6 h. After cooling to 0-5°C the mixture is filtered, the solid obtained washed with 500 mL of absolute ethanol under reflux and dried at 80°C in a vacuum oven to yield 83 g (83%) of the product of the title.

NMR ^1H (DMSO), δ (ppm): 6.4 (s, 2H, $-NH_2$), 6.5-7.0 (s, 2H, $-NH_2$), 7.3-7.5 (m, 2H, ArH), 7.7 (d, 1H, ArH). M.p.= 217°C.

Purity (HPLC): exceeds 99.9%.

Example 4: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

Following the method described in Example 3, but using 1200 mL of isopropyl alcohol instead of the 1000 mL of ethanol, 90 g (90%) of the product of the title is obtained.

Example 5: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

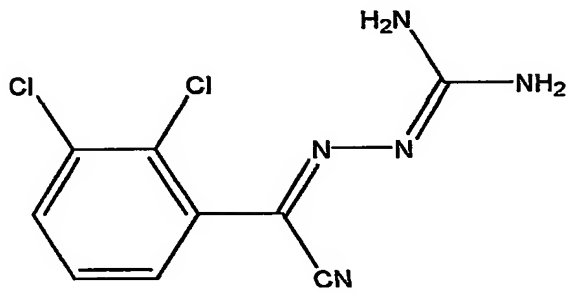
Following the method described in Example 3, but using 500 mL of isopropyl alcohol and 188 mL of water instead of the 1000 mL of ethanol, 82 g (82%) of the product of the title is obtained.

Example 6: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

Following the method described in Example 3, but using ethanol 96% instead of ethanol, 90 g (90%) of the product of the title is obtained.

C L A I M S

1. A process for preparing the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, of formula (II):



(II)

which comprises the reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate, **characterised** in that it is carried out in non-aqueous medium in the presence of methanesulphonic acid.

2. Process according to Claim 1, characterised in that said reaction is carried out within a temperature range of 20 to 80°C.

3. Process according to Claim 2, characterised in that said reaction is carried out within a temperature range of 30 to 60°C.

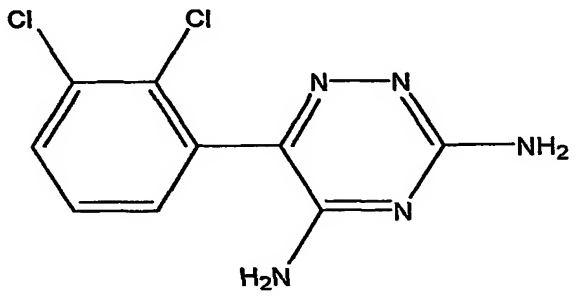
4. Process according to Claim 1, characterised in that, once the reaction has finished, it comprises an additional step that consists in:

i) addition of water; and

ii) adjustment of the pH of the medium until a pH higher than the pKa of the hydrogen cyanide is achieved.

5. Process according to Claim 4, characterised in that in ii), said adjustment of the pH is carried out by adding a sodium hydroxide solution.

6. Process for preparing the 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, which comprises the following steps:

a) preparation of the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, of formula (II), according to any of claims 1 to 5;

b) cyclisation of said intermediate of formula (II) in an aliphatic alcohol or in an aliphatic alcohol/water solution under reflux; and,

if desired, obtaining a pharmaceutically acceptable salt thereof.

7. Process according to Claim 6, characterised in that said aliphatic alcohol used in step b) may be chosen from between ethanol and isopropanol.

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